Epigenetics Overview

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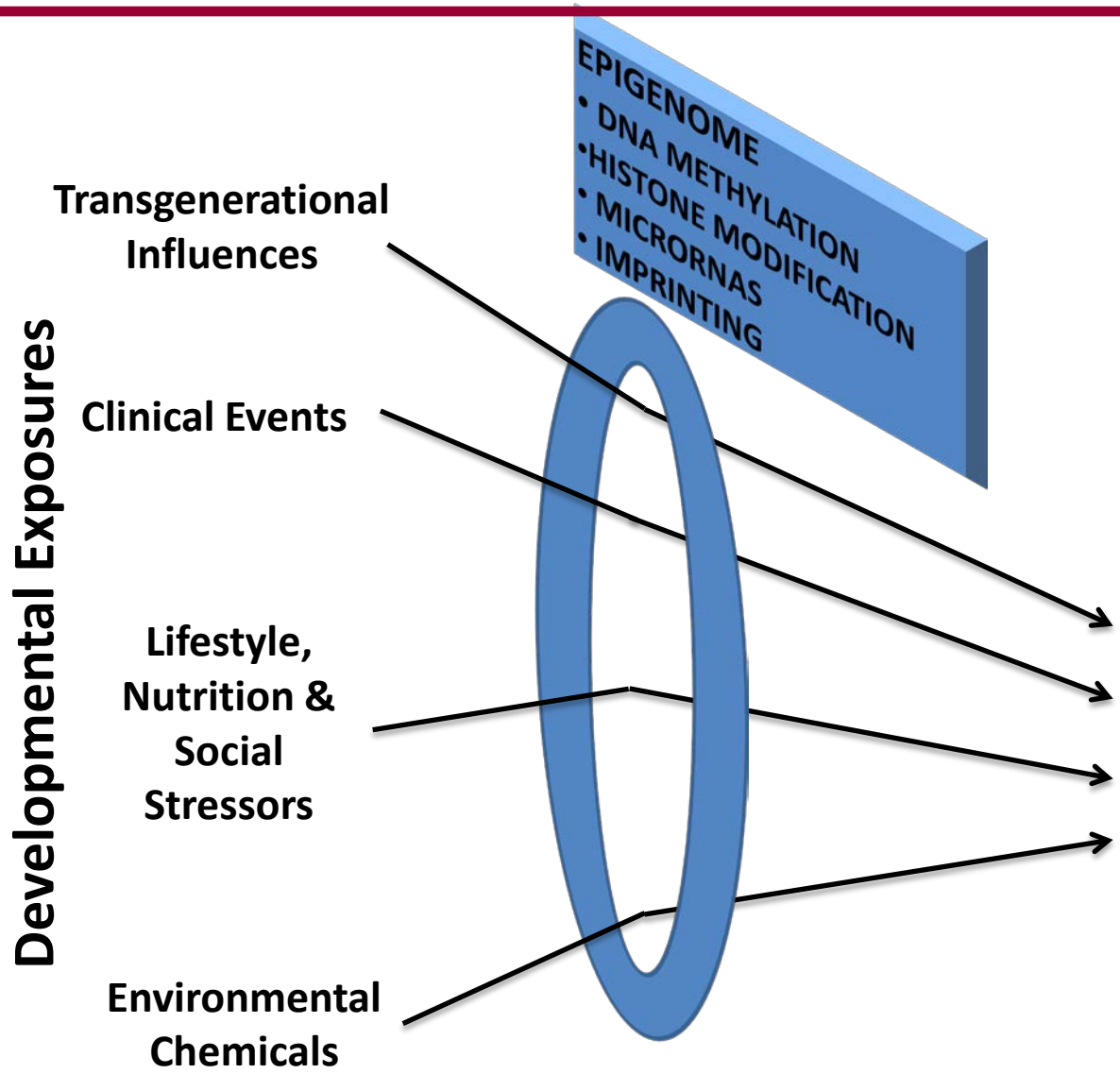
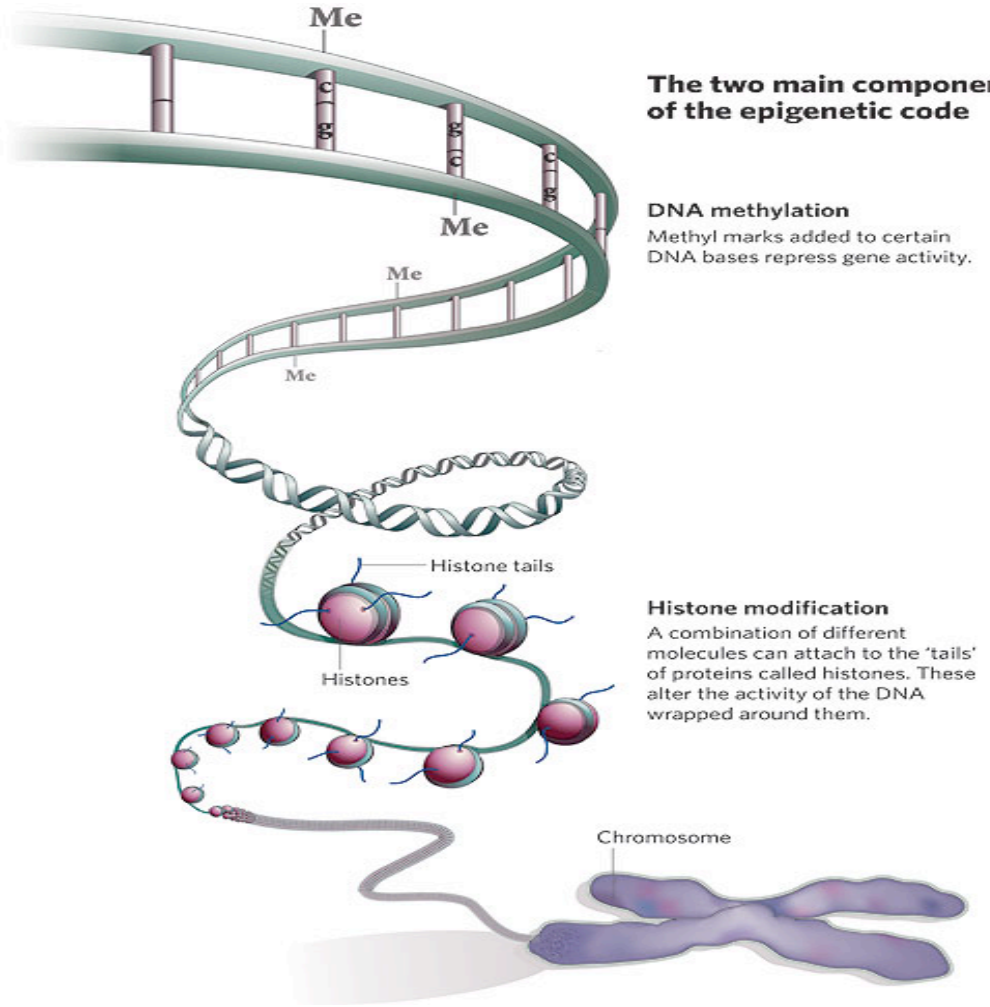
I have funding from NIEHS, USEPA, and the American Chemistry Council. I am an occasional expert consultant for chemical and pharmaceutical companies, and own stock in CytoSolv, an early stage biotechnology company developing a wound healing therapeutic.



Later Life Outcomes and Susceptibilities

- Growth
- Neurobehavior
- Reproduction
- Obesity
- Cancer

Developmental Origins of Health and Disease



The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.

http://embryology.med.unsw.edu.au/MolDev/epigenetic.htm

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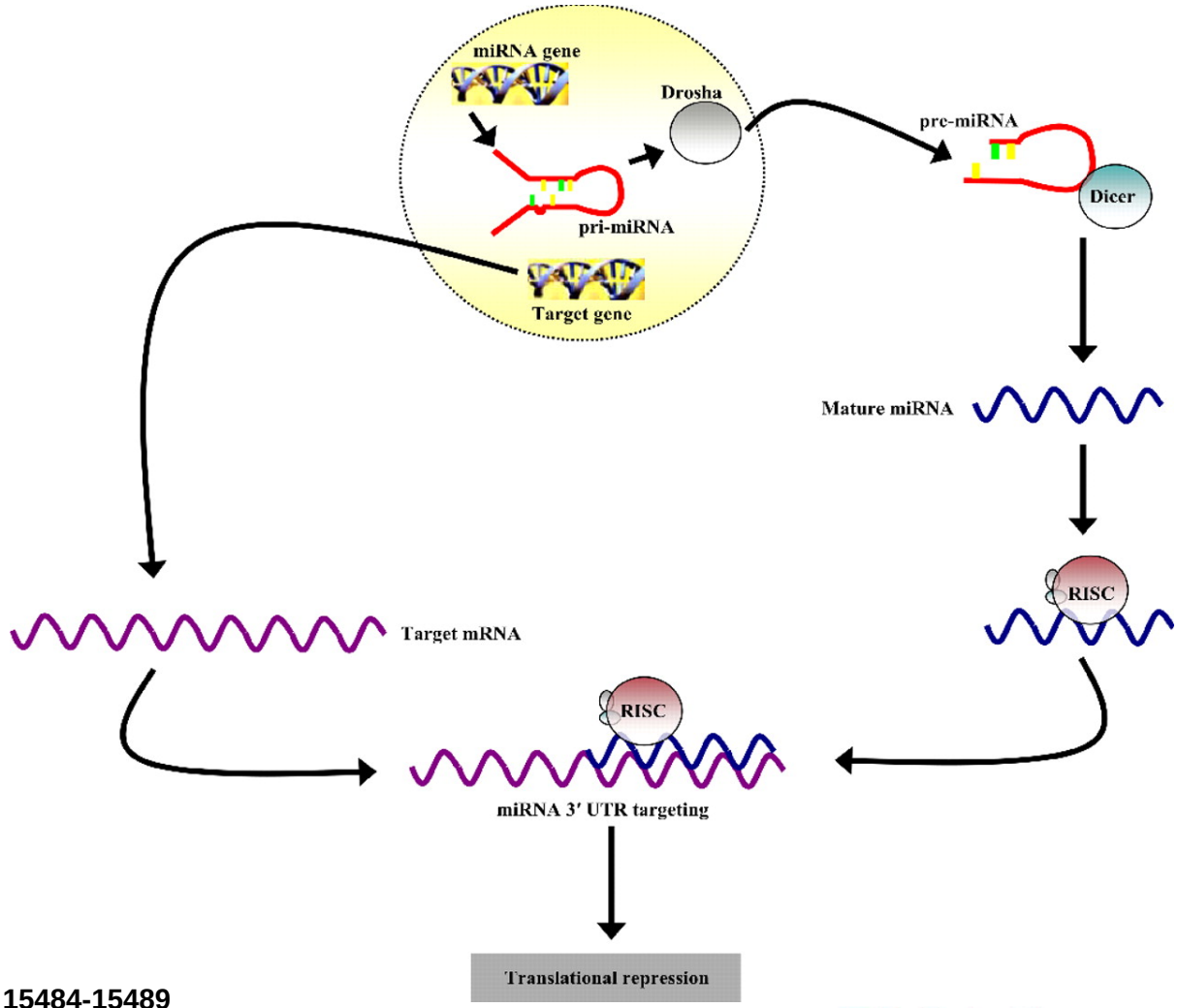
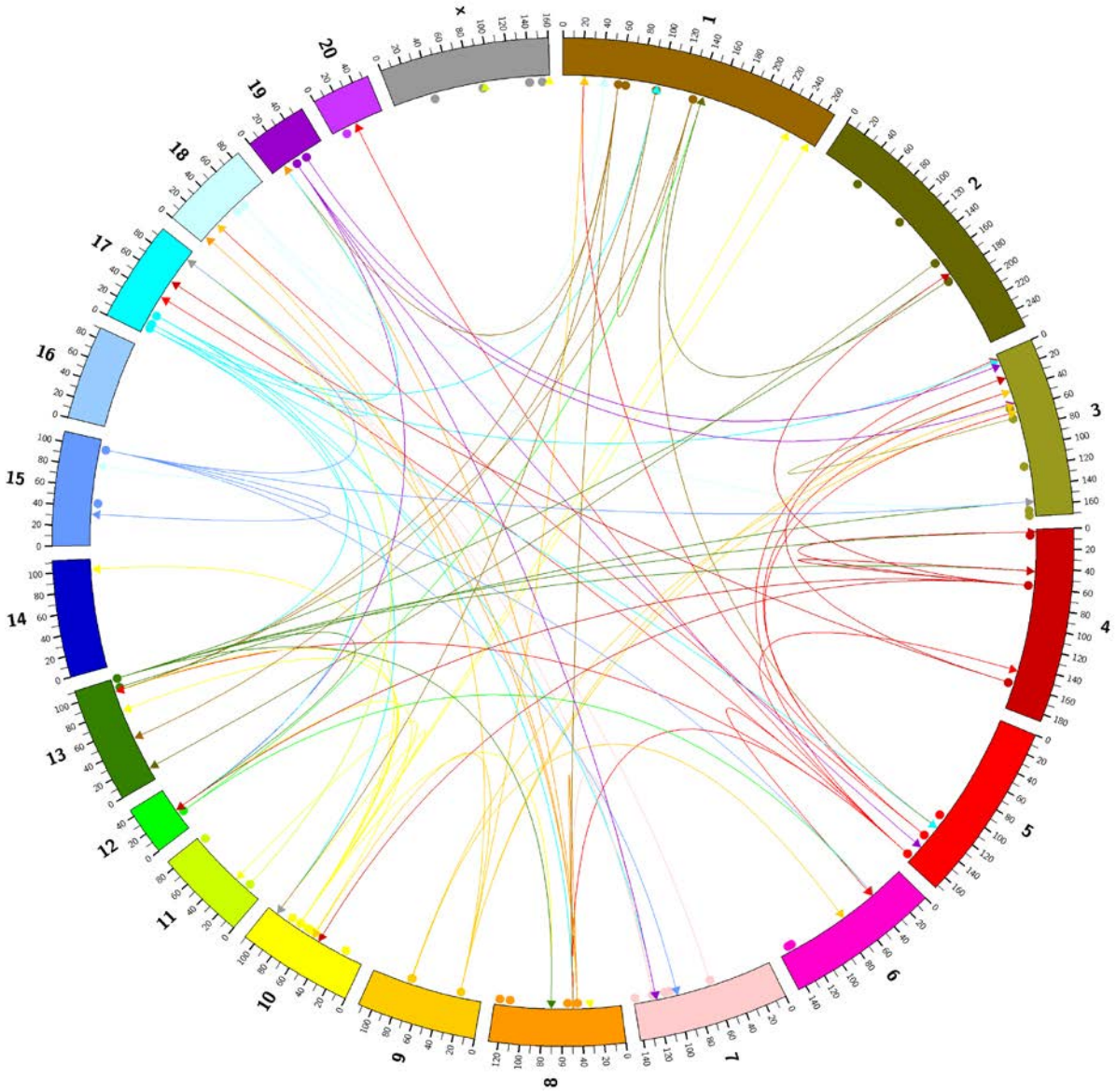
Cartoon depicting the mechanism of miRNA transcription, processing, and regulatory activity. miRNA genes are transcribed by RNA polymerase II to form primary miRNA (pri-miRNA) molecules



Greco S J , Rameshwar P PNAS 2007;104:15484-15489

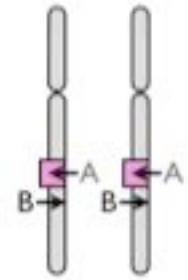
PNAS

Formative Center for the Evaluation of Environmental Impacts on Fetal Development

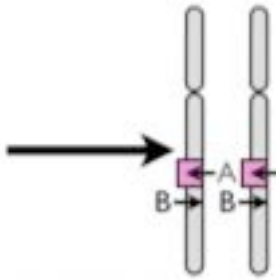


Imprinting

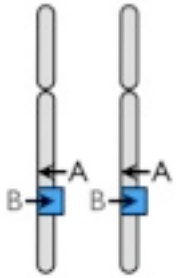
Female Adult
A active, B suppressed



Egg

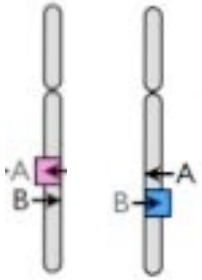


Male Adult
A suppressed, B active



Sperm

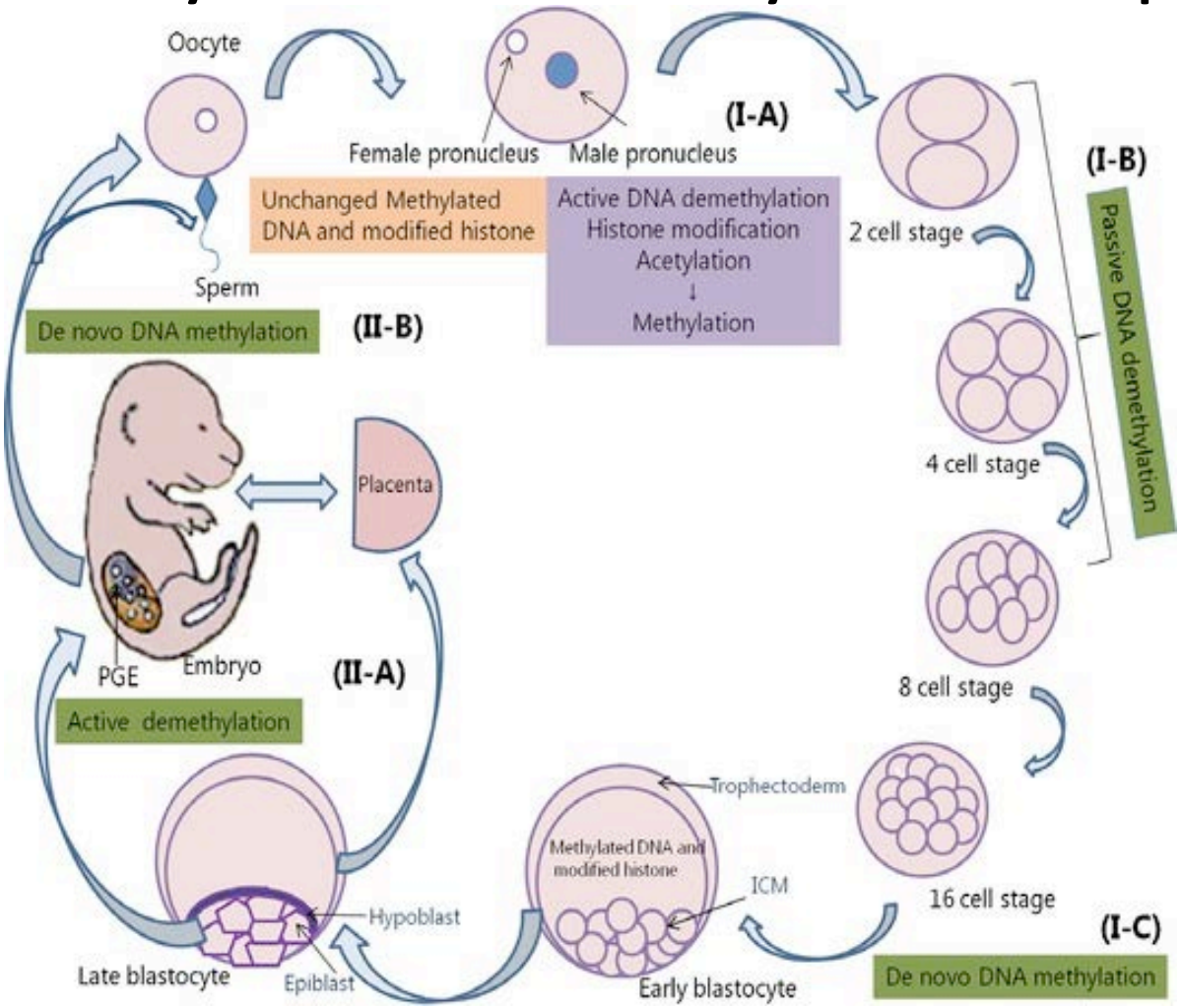
Zygote



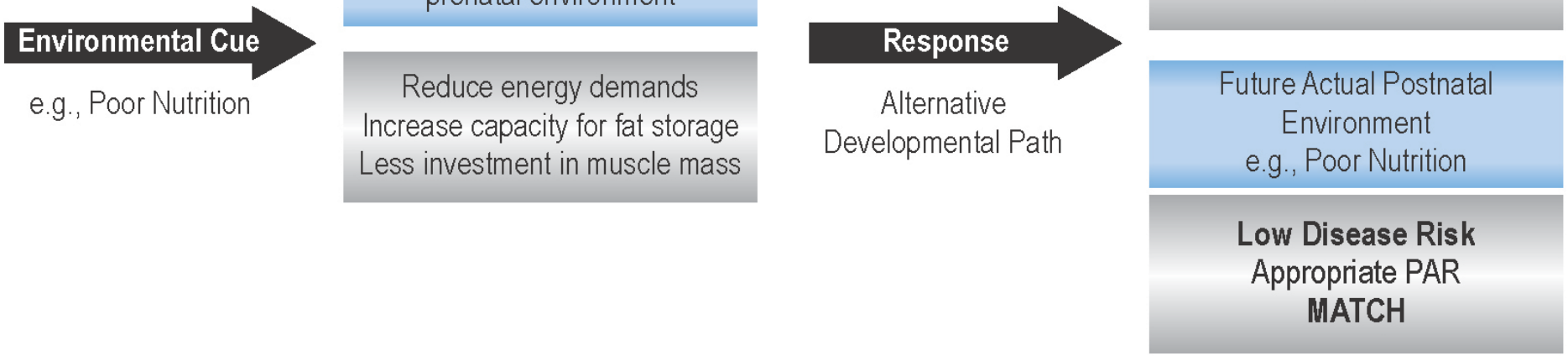
Allele A is paternally imprinted

Erasure and re-imprinting in the germ line according to the offspring sex

DNA Methylation in Embryo Development



http://www.springerimages.com/Images/Biomedicine/1-10.1007_s13148-010-0016-0-1

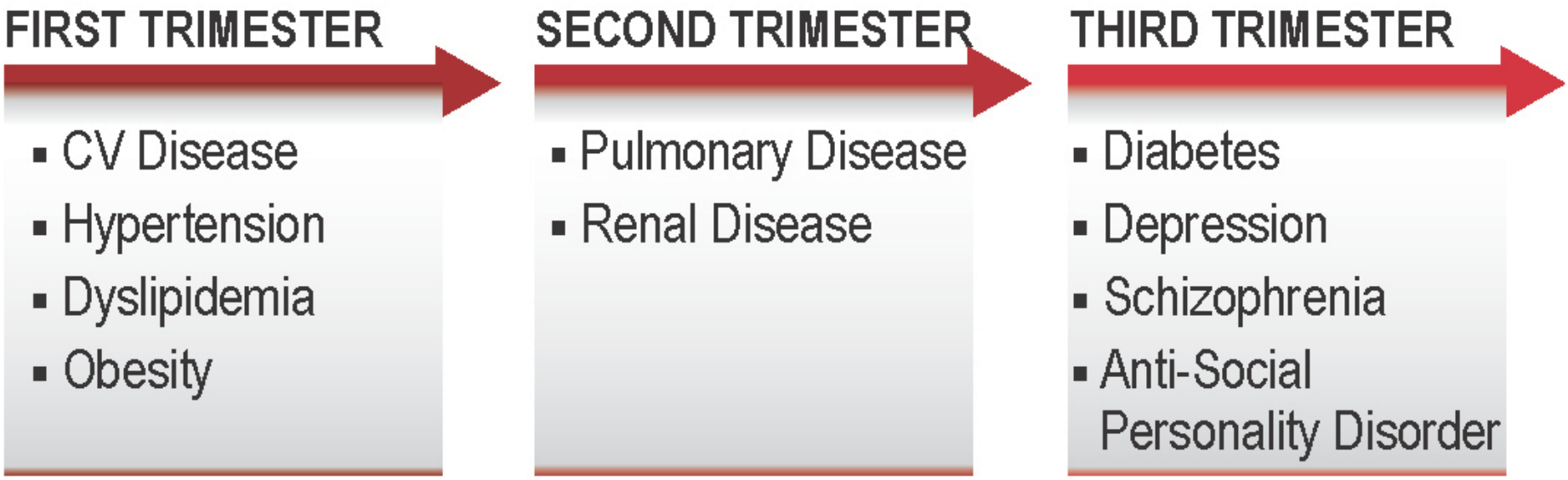

Environmental Cue
e.g., Poor Nutrition
Developmental Plastic Stage
"prenatal environment"
Reduce energy demands
Increase capacity for fat storage
Less investment in muscle mass
Response
Alternative
Developmental Path
Future Actual Postnatal
Environment
e.g., High-Calorie Diet
Increased Disease Risk
Inappropriate PAR
MISMATCH
Future Actual Postnatal
Environment
e.g., Poor Nutrition
Low Disease Risk
Appropriate PAR
MATCH

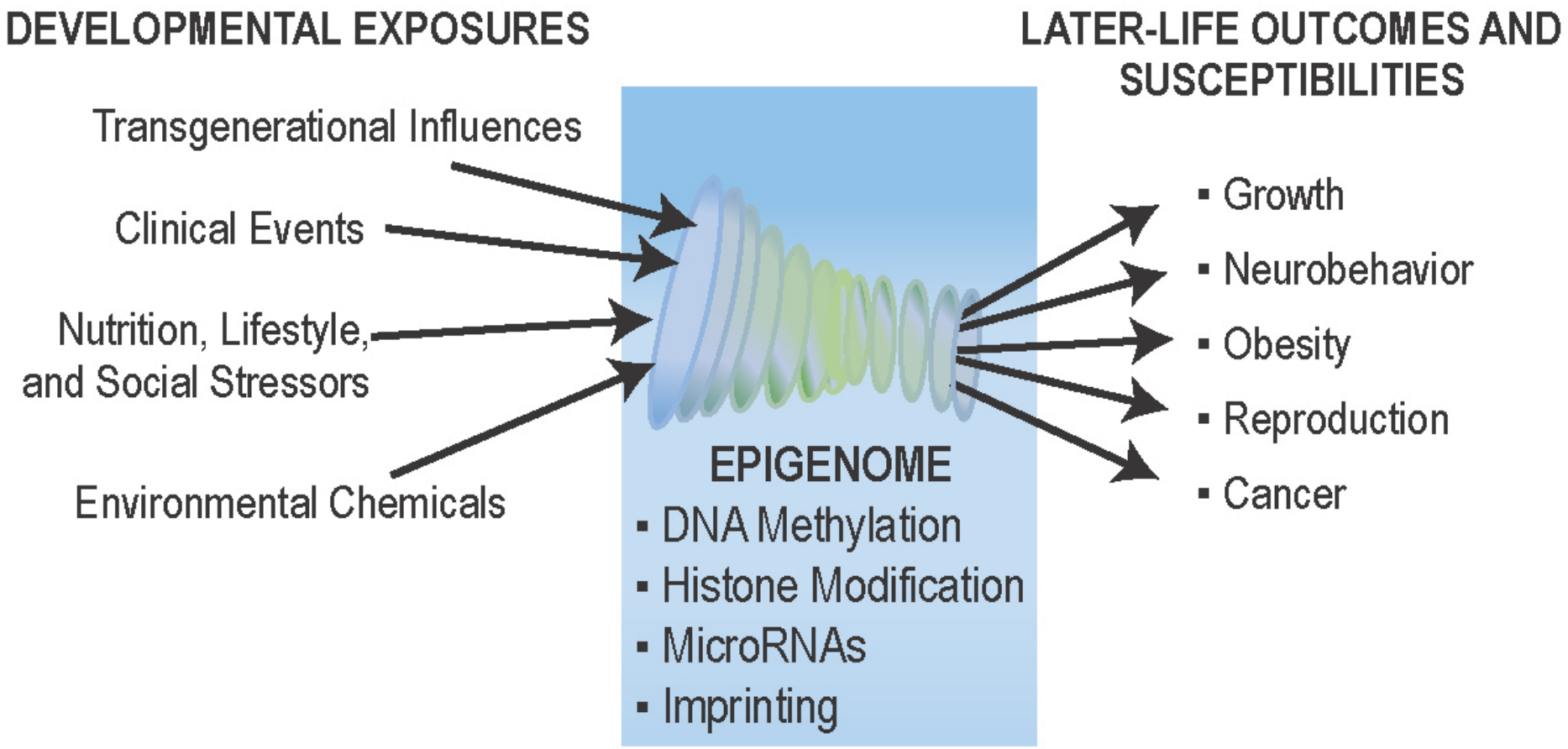
Autumn 1944 – Western Holland was blockaded by the Nazis, who turned away all shipments. Led to a food shortage during one of Europe's coldest winters.

Nutrition and Chronic Disease

- The Dutch survived on < 500 calories/day - ¼ of pre-war consumption
- Food restriction in-utero had dramatic consequences to those born to mothers who survived the Hunger Winter
- Among >800 individuals born during the siege:
  - More obesity, diabetes, heart disease, higher blood pressure, hypercholesterolemia, and reduced glucose tolerance

Data suggests a link between in-utero deprivation, abundant nutrient supply after birth, and chronic disease – particularly heart disease.


FIRST TRIMESTER
CV Disease
Hypertension
Dyslipidemia
Obesity
SECOND TRIMESTER
Pulmonary Disease
Renal Disease
THIRD TRIMESTER
Diabetes
Depression
Schizophrenia
Anti-Social Personality Disorder


DEVELOPMENTAL EXPOSURES
Transgenerational Influences
Clinical Events
Nutrition, Lifestyle, and Social Stressors
Environmental Chemicals
EPIGENOME
▪ DNA Methylation
▪ Histone Modification
▪ MicroRNAs
▪ Imprinting
LATER-LIFE OUTCOMES AND SUSCEPTIBILITIES
▪ Growth
▪ Neurobehavior
▪ Obesity
▪ Reproduction
▪ Cancer

- Dose considerations (non-monotonic effects, timing, tissue of exposure)
- Challenges and opportunities for epigenetic epidemiology
- Does an epigenetic change necessarily lead to an adverse effect?
- Quantitative validation following whole-epigenome analysis
- How can epigenetics biomarkers be used to identify mechanisms, so that we can treat the cause and not the symptom?
- Can epigenetic biomarkers be used as integrative measures of mixed exposures?
- How do we assess the volumes of information stored in the histone code?
- How do we prioritize the different epigenetic findings across the whole genome?
- What are the most critical developmental time points for producing a later life effect of an exposure?
- What are non-epigenetic mechanisms by which early life events alter adult disease risk, and are there early markers for these?
- How relevant is gender and tissue specificity?